

Diffusion and interfaces in pattern formation

Ovidiu Radulescu¹, Sergei Vakulenko²,

¹IRMAR, UMR CNRS 6625, Université de Rennes 1, France

²Institute for Mech. Engineering Problems Sanct Petersburg, Russia

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Abstract

We discuss several qualitative properties of the solutions of reaction-diffusion systems and equations of the form $u_t = \epsilon^2 D \Delta u + f(u, x, \epsilon t)$, that are used in modeling pattern formation. We analyze the diffusion neutral and the diffusion dependent situations that, in the time autonomous case, are distinguished by considering the attractors of the shorted equation $u_t = f(u, x)$. We discuss the consequences of being in one or in the other of the two situations and present examples from developmental biology and from fluid mechanics.

1 Introduction

Mathematical models in developmental biology [WBJ02, MSR91, RS95] and in the theory of phase transitions [AC79, Pom86, ROL99], lead to reaction-diffusion equations with a spatial inhomogeneous reaction term of the form $u_t = D \Delta u + f(u, x)$. There are two different fundamental concepts on the role of diffusion in development (patterning) and, respectively, two different approaches.

The first, more mathematical, approach is pioneered by the work of Turing [Tur52] and developed by many authors (see, for example, [Mei82, Mur93]). For Turing's patterning mechanisms [Tur52, Mei82] a spatial dependence of the reaction term $f = f(u, x)$ is not necessary. Conditions on diffusion coefficients and on reaction terms are needed in order to have spontaneous translation symmetry breaking by developing periodic patterns from a homogeneous state [Hun99].

The second approach is inspired from the ideas of the 19th century biologist Hans Driesch who pointed out that the fate of a cell can be determined by its position inside the embryo. Later, it has been shown that differentiation is connected with reading an inhomogeneous level (gradient) of maternal proteins (morphogens). Wolpert [WBJ02, Wol70] coined the term "positional information" and gave the theoretical basis of gradient models. In a short discussion of morphogenesis, René Thom [Tho68] proposed that spatially inhomogeneous reaction-diffusion equations can model formation of patterns containing interfaces. He pointed out that interfaces are placed according to the Maxwell rule [Tho68, Pom86, ROL99]. Nevertheless, biologists seem to reject the role of diffusion in Wolpert's mechanism. This belief is backed up by the fact that

without diffusion monotone morphogen profiles can induce complex layered patterns consisting of many narrow interfaces [WBJ02]. In fact, one can show that patterns of arbitrary complexity can be generated by the diffusionless Wolpert mechanism [VG03b, VG03a].

Turing and Wolpert type mechanisms are not restricted to developmental biology. They apply to other pattern formation phenomena. Thus, in material science and fluid mechanics Cahn's spinodal instabilities are similar to Turing instabilities from biology and can be modeled by space homogeneous partial differential equations [CH58]. Other examples of Wolpert-like mechanisms can be found in fluid mechanics. Flow-induced phase transitions can trigger the formation of bands separated by narrow interfaces [ORL00, ROL99, RO00, ROD03].

These examples suggest that interfaces play an important role in patterning. An interface can be defined as a region of strong inhomogeneity. Fick's law implies that diffusion is important at interfaces, but it says nothing on the role of diffusion for the control of the interface position and dynamics. In particular, how do the patterns behave in the limit of vanishing diffusion?

Two distinct situations are considered here. In the first situation, patterning follows essentially from the nonlinearity of the reaction term and does not suffer qualitative changes in the limit of vanishing diffusion. The corresponding patterning mechanism will be called diffusion neutral. In the second situation, patterning depends essentially on diffusion and the patterning mechanism will be called diffusion dependent. These two types of patterning are related to two different situations and, respectively, two types of interfaces.

The first situation can appear, for example, when dynamics of a "shorted system" (where the diffusion is removed) has, as a global attractor, for any values of space variables x , a stable rest point (depending on x). In this case, theorems on a connection between shorted system and the original reaction diffusion system are established. The interface existence results from the steep spatial dependence of the reaction term on x .

The second situation arises, when the two local attractors coexist. In this case, patterning cannot be diffusion neutral and thus it is incorrect to remove the diffusion in the equations. Here an interface appears as a localized jump in space from one attractor to another.

There exists a rather well developed mathematical theory for the second situation in the one-component case (see [CP89, Fus90, Fif89, MV88] among many others), if local attractors are rest points. In this case the interfaces are well localized traveling wave solutions of singularly perturbed reaction-diffusion equations. Stationary patterns are formed by interfaces corresponding to zero velocity traveling waves. Such stationary interfaces occur in many systems and they are well represented in biology (see [Mur93]) and in the phase transition theory [ORL00, ROL99, RO00, ROD03, Pom86]. Their existence is well known for reaction-diffusion equations with a typical bistable nonlinearities and for some reaction-diffusion systems [VVV94, VV96, VV99]. Unfortunately, up to now there is no general theory for systems of reaction-diffusion equations, except for rather restrictive situations (gradient systems and monotone systems, [VVV94, VV96, VV99]).

Notice that interfaces can interact one with another. Under some conditions, one can reduce the pattern dynamics (that is a dynamics in an infinite dimensional space) to the finite dimensional dynamics of a set of interacting interfaces [MV88, CP89, Fus90]. If this reduction is possible, the result is a simplification

of pattern time evolution. Instead of direct numerical simulation of patterning, one can study time evolution of interfaces that can be described by ordinary differential equations (instead of partial differential equations). In many cases, these ordinary equations can be resolved analytically. In this paper we also give new results on interface motion and apply these results to genetic circuits and to fluid mechanics.

2 Statement of the problem

We study initial value boundary problems for the following reaction-diffusion systems:

$$u_t = \epsilon^2 D \nabla^2 u + f(u, x, \epsilon t), \quad (2.1)$$

where $u = u(x, t) \in \mathbf{R}^n$ is an unknown vector function, $x \in \Omega \subset \mathbf{R}^q$, where Ω is a compact domain with a regular boundary $\partial\Omega$, $t \geq 0$. In equation (2.1), D is a diagonal matrix with positive entries, i.e., $D = \text{diag}\{d_1, d_2, \dots, d_n\}$, ϵ is a parameter for diffusion intensity, f is a reaction term depending, in general, on x and also slowly on time. Initial data has the following form

$$u(x, 0) = u_0(x). \quad (2.2)$$

In applications, boundary conditions are usually of the Neumann type. This means that there is no flux across the boundary:

$$\nabla u(x) \cdot n(x) = 0, \quad x \in \partial\Omega, \quad (2.3)$$

where $n(x)$ is an unit normal vector to the boundary at x . This work is focused on internal layers, and to avoid complicated problem connected with boundary layers, we sometimes consider a simplified problem, when Ω is a box in \mathbf{R}^q , with periodical boundary conditions in x .

In this paper we refer to the gene circuit model proposed to describe early stages of *Drosophila* (fruit-fly) morphogenesis [MSR91, RS95]. In this model the reaction term takes a special form (that reminds the Hopfield neural network model):

$$f_i = \sigma_\alpha \left(\sum_{j=1}^n K_{ij} u_j + \sum_{k=1}^p J_{ik} m_k(x) - h_i \right) - \lambda_i u_i, \quad (2.4)$$

where u_j are zygotic gene concentrations, K is a matrix describing pair gene interaction between zygotic genes, J is a matrix describing pair interaction between zygotic genes and maternal genes, h_i are thresholds, m_i are functions of x which define maternal gene concentrations (morphogen gradients). Here $\sigma_\alpha(h) = \sigma(\alpha h)$, σ is a monotone and smooth (at least twice differentiable) "sigmoidal" function such that

$$\sigma(-\infty) = 0, \quad \sigma(+\infty) = 1. \quad (2.5)$$

The function σ_α becomes a step-like function as its sharpness α tends to ∞ . Typical examples can be given by

$$\sigma(h) = \frac{1}{1 + \exp(-h)}, \quad \sigma(h) = \frac{1}{2} \left(\frac{h}{\sqrt{1 + h^2}} + 1 \right). \quad (2.6)$$

Slow dependence of K, J, h, λ on time can be also considered.

Our second example is a generalization of the Allen-Cahn model of phase transitions. The spatial homogeneous version of this model has been discussed in connection to equilibrium first order phase transitions [AC79], population dynamics [GM77], metastability phenomena [CP89, Pin01]. It has been used as a toy model to describe shear banding of complex fluids [ROL99]. The spatial inhomogeneous model can be described by the following reaction-diffusion equation with Neumann no flux boundary conditions on some compact set $\Omega \subset \mathbf{R}^q$:

$$u_t = \epsilon^2 u_{xx} - A^2(x, \tau)[u - u_0(x, \tau)][u - u_2(x, \tau)][u - u_1(x, \tau)], \quad (2.7)$$

where $\tau = \epsilon t$, $u_0(x, \tau) < u_2(x, \tau) < u_1(x, \tau)$ and $u_i(x, \tau), A(x, \tau) > 0$ are smooth (at least C^2), real functions.

2.1 Main ideas

We are interested in the influence of diffusion on patterning. We shall call a pattern formation mechanism "diffusion neutral", if the solution $u^\epsilon(x, t)$ of system (2.1) converges uniformly to a pattern $v(x, t)$ that can be found in absence of diffusion, as the diffusion coefficients converge to zero. In this case the diffusion term is a regular perturbation. The pattern formation is "diffusion dependent", if this does not hold.

More precisely, let us formulate the following definition.

Let $u^\epsilon(x, t)$ denote the solution of reaction-diffusion system (2.1) with Neumann conditions (2.2) or with periodical boundary conditions in x on $\Omega = [0, 1]^q$ and initial data $u^\epsilon(x, 0) = u_0(x)$.

Let us introduce the following system of ordinary differential equations (we shall refer to it as the "shorted" system):

$$v_t = f(v, x, t), \quad v(x, 0) = u_0(x). \quad (2.8)$$

Definition. *Patterning defined by problem (2.1), (2.2) with initial data $u_0(x)$ is diffusion neutral, if the estimate*

$$|u^\epsilon(x, t) - v(x, t)| < r_\epsilon$$

holds for any $x \in \Omega, t > 0$, where $r_\epsilon \rightarrow 0$ as $\epsilon \rightarrow 0$. The number r_ϵ is independent of x, t but can depend on initial data. Otherwise, patterning is diffusion dependent.

Notice that patterning can be diffusion neutral or diffusion dependent depending on initial data $u_0(x)$.

In biological axial morphogenesis and fluid mechanics shear induced phase transitions, typical patterns are segmented, with narrow interfaces between segments [WBJ02, ROL99]. We show that the "diffusion neutral" and "diffusion dependent" situations correspond to two different types of interfaces. To illustrate the main ideas, let us consider the one-dimensional and one-component case. ($q = 1, n = 1$).

Stationary patterns

An important situation in pattern formation is the case, where system (2.1) has steady state solutions. In biology, steady states are always approximations, valid within a certain time scale. In order to study stationary patterns, let us consider the autonomous case of system (2.1), where f does not depend on t .

There occur two essentially different cases that are illustrated in Fig.2.1:

Case I. For any x , the shorted equation has a unique point attractor $v = \phi(x)$, where ϕ is a solution of the equation $f(\phi(x), x) = 0$. This attractor, for each x , attracts globally all trajectories of the shorted system.

For small ϵ , the solution $u^\epsilon(x, t)$ is close to the solution $v(x, t)$ of the shorted equation. This function v tends to $\phi(x)$ for large times. In this case a narrow interface can occur only if the function $f(\phi, x)$ is, in a sense, "sharp" in x . We shall refer to such a region as type 1 interface or "transition layer", because the variations of one or several components of the function $\phi(x)$ are strong across it. It is the case, for example, if, in the Eq. (2.4), the parameter α is large. For $n = p = q = 1$, $J_{11}m_1(x) = kx$, $K_{11} = 0$, the solution ϕ has the following form

$$\phi(x) = \frac{A}{1 + \exp(-\alpha(kx - h_1))}, \quad A > 0. \quad (2.9)$$

This solution describes an interface at $x = h_1/k$ whose width is $1/(k\alpha)$.

Case II. There exist intervals in x , where the shorted equation $f(u, x) = 0$ has several different attractors, for example $\phi_1(x), \phi_2(x), \dots, \phi_k(x)$. The interfaces correspond to a localized jump from an attractor to another one, the functions $\phi_k(x)$ having otherwise slow variation. In this case interfaces have widths of order ϵ , and are diffusion controlled. We shall refer to these as type 2 interfaces or "diffusion layers".

In the case II, diffusion neutral patterning is possible if initial data $u_0(x)$ lies in an attraction basin of only one attractor, for instance $\phi_1(x)$. If initial data lies in the attraction basins of different attractors, the pattern contains internal layers and patterning is diffusion dependent. For small ϵ , the solution $u^\epsilon(x, t)$ is close to the solution of the shorted equation only for times $\mathcal{O}(-\log(\epsilon))$. The dynamics is diffusion dependent because, in the absence of diffusion the derivatives of the solution of the shorted equation increase unboundedly at some x [MV88]. We can identify these x with the initial positions of the diffusion layers.

In the presence of diffusion, interfaces move toward diffusion controlled equilibrium positions that are generally different from the positions in the absence of diffusion [FH88, ROL99, RO00]. Let us notice that the steady state solutions of the shorted equation can have an arbitrary number of interfaces in arbitrary positions determined by the sequence of attractor basins to which the initial data belongs to. With diffusion, there are restrictions on the number and on the positions of the interfaces [RO00].

2.2 Main results

Our main result for diffusion neutral patterning are Theorems 3.1 and 3.2 that will be formulated in the next section. Let us summarize this result here. Let us suppose that in the autonomous case $f = f(u, x)$ shorted system (2.8) has only the point attractors (equilibria) $\phi_k(x)$, with open attraction basins $B_k(x)$ for all x . The case of bifurcations and turning points, where several curves $\phi_k(x)$ touch one another [Tho68] needs special treatment and will not be considered in this paper. Furthermore, let us assume that the initial data $u_0(x)$ is contained in $B_1(x)$ for any x . Then the solution $u^\epsilon(x, t)$ of system (2.1) with periodic boundary conditions stays, for all times t , in a small neighborhood of the solution

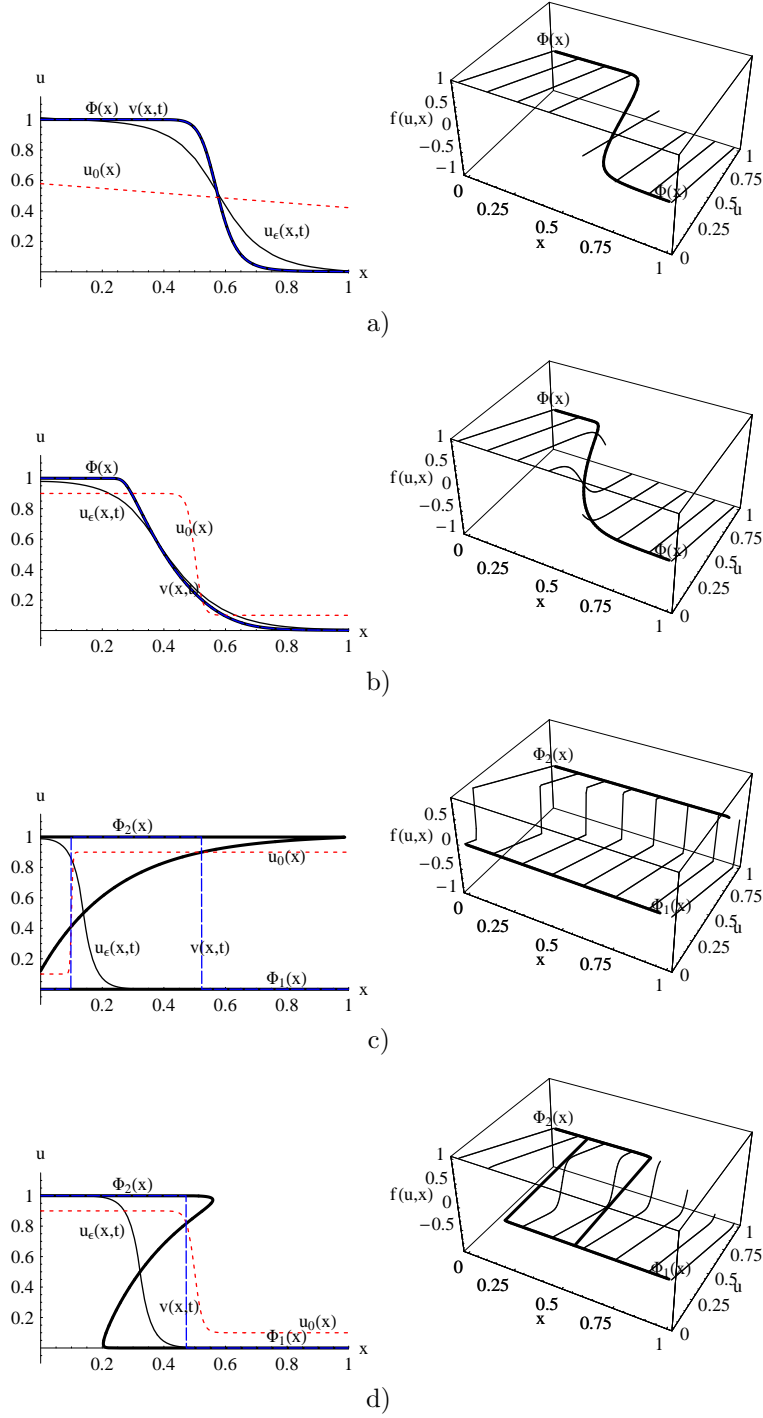


Figure 1: Gene circuit model for $n = 1, p = 1, q = 1, \sigma_\alpha(x) = 1/(1 + \exp(-\alpha x)), m(x) = \exp(-x)$. Diffusion neutral patterning: a) $\alpha = 80.0, K_{11} = 0, J_{11} = 1.0, h_1 = 0.1, \epsilon^2 = 0.1$. b) $\alpha = 80.0, K_{11} = -0.2, J_{11} = 1.0, h_1 = 0.1, \epsilon^2 = 0.1$. Diffusion dependent patterning: c) $\alpha = 400.0, K_{11} = 1.7, J_{11} = 1.5, h_1 = 1.71, \epsilon^2 = 0.001$. d) $\alpha = 80.0, K_{11} = 0.45, J_{11} = 1.0, h_1 = 0.5, \epsilon^2 = 0.001$. The solution $u_\epsilon(x, t)$ of the reaction-diffusion equation and the solution $v(x, t)$ of the shorted equation are represented after a large time when the pattern is practically at the attractors. In the diffusion dependent case, depending on initial data u_0 the solution $v(x, t)$ of the shorted equation can have many interfaces (two in c)).

$v(x, t)$ of the shorted system. Naturally, $v(x, t) \rightarrow \phi_1(x)$ and, therefore,

$$u^\epsilon(x, t) = \phi_1(x) + o(\epsilon^s), \quad \epsilon \rightarrow 0, s > 0 \quad (2.10)$$

for sufficiently large $t > t_\epsilon$.

Let us consider now the diffusion dependent patterning. Recently it has been shown that reaction-diffusion systems can generate any structurally stable dynamics. This result holds even for the two component case, if f is allowed to depend on x [Vak97, Vak00]. Arbitrarily complex dynamics can be reproduced by genetic circuit systems defined by systems (2.1) with nonlinearities (2.4) [FN93, Vak02]. Furthermore these systems are capable to produce any space-time patterns depending on the parameters n, K, h [VG03a, VG03b].

If, for some x , the shorted system possesses stable limit cycles or chaotic attractors, we can prove only a weak variant of Theorem 3.1, where u^ϵ stays close to v only on a large but bounded time interval $O(-\log \epsilon)$. It is difficult to say something beyond this interval. If the attractor of the shorted system is a stable limit cycle, rigorous results are unknown, however, a formal asymptotic solution can be obtained by the Kuramoto method [Kur84]. This solution shows that, for generic initial data, patterning is diffusion dependent. Nothing is known on the structure of the solution u^ϵ for chaotic attractors. However, taking into account that such attractors contain many periodic trajectories, one can suppose that in this case patterning is diffusion depending as well.

An interesting situation arises if initial data u_0 can lie, for different x , in attraction basins of different attractors $\phi_k(x)$. For systems we prove here a general theorem which shows that in this case patterning is diffusion dependent, but it is difficult to describe patterning analytically.

An analytical approach is possible for reaction-diffusion equations. The general case of reaction-diffusion equations with a spatial inhomogeneity has been considered by [Fif89, FH88]. These works gave a description of stationary internal layers and convergence to these layers. Our Theorem 5.2 extends some results of [Fif89]. For the one-component, one-dimensional patterning problem we prove existence of traveling waves in the bistable case and we reduce the patterning dynamics to a differential equation for the position of the inner layer. We also include a slow time dependence of the reaction term on timescales slower than the diffusion time.

3 Diffusion neutral patterning

First, let us we formulate some assumptions.

Suppose that the reaction term f is a C^2 regular function of x, u and the initial data u_0 have at least C^2 -regularity on the domain Ω . Let us consider the case when Ω is a compact box in \mathbf{R}^m and let us set periodical boundary conditions along all its edges.

Our next assumption is concerned with the attractors and the attractor basins of shorted system (2.8). Notice that (2.8) is a system of ordinary differential equations in \mathbf{R}^n whose right hand sides and initial data involve x as a parameter. Let us assume that for each x dynamics (2.8) is dissipative, i.e., there exists a ball B_R of a radius R centered at $v = 0$ and this ball is a globally attracting set. This is the case, for example, if there holds the following

Dissipativity condition for shorted system: *For any $x \in \Omega$ there exists a positive number $R(x)$ such that*

$$u \cdot f(u, x) < 0 \quad (|u| = R(x), x \in \Omega) \quad (3.1)$$

Sometimes we shall use the stronger

Uniform Dissipativity condition: *There exists a positive number R_0 such that for any x*

$$u \cdot f(u, x) < 0 \quad (|u| = R_0, x \in \Omega) \quad (3.2)$$

This assumption guarantees existence and uniqueness of solutions of the problem (2.1),(2.2). It is easy to show that this condition holds for genetic circuits.

Let us recall the definition of local attractor and of their attraction basin for dissipative systems of ordinary differential equations. Let us assume that the dissipativity condition holds. For a fixed x , the set \mathcal{A}_x is a local attractor for the shorted system, if this set has an attraction basin $B(\mathcal{A}_x)$ containing an open neighborhood V_x of \mathcal{A}_x . The attraction basin $B(\mathcal{A}_x)$ consists of all $u_0(x)$ such that the trajectory $u(t, x, u_0(x))$ starting at $u_0(x)$ approaches to \mathcal{A}_x for large times:

$$\text{dist}[u(t, x, u_0(x)), \mathcal{A}_x] \rightarrow 0 \quad (t \rightarrow \infty).$$

Suppose among the local attractors of (2.6) there exists at least one isolated branch (parametrized by x) of point attractors $\mathcal{A}_x = \{\phi(x)\}$. This means that $\phi(x)$ are stable steady states of the shorted system.

Attraction basin condition: *Suppose that for each x there is a point attractor $\mathcal{A}_x = \{\phi(x)\}$ of the system (2.8). Moreover, assume that the initial data $u_0(x)$ lie, for all x , in the corresponding basin $B(\mathcal{A}_x)$:*

$$u_0(x) \in B(\mathcal{A}_x) = B(\{\phi(x)\}). \quad (3.3)$$

Let us formulate a condition for the stability of \mathcal{A}_x . Let $M(x)$ be the derivative of f at $\phi(x)$:

$$f(\phi + w, x) - f(\phi, x) = M(x)w + h(w, x), \quad |h| < C|w|^2 \quad (3.4)$$

for small w and some constant C . Suppose that there holds the following

Strong linear stability assumption: *For any $x \in \Omega$ the corresponding matrix $M(x)$ at $\phi(x)$ satisfies the following condition:*

$$\sum_{j \neq i} |M_{ij}(x)| + M_{ii}(x) \leq -b < 0. \quad (3.5)$$

This condition ensures that the spectrum of the matrix $M(x)$ lies in the negative half-plane being separated by a gap from the imaginary axis. This gap is uniform in x due to the compactness of Ω . Hence, $\{\phi(x)\}$ has an open attraction basin B_x for all x .

We can state now

Theorem 3.1. *Let $f = f(u, x)$ and u_0 are sufficiently smooth as formulated above.*

Under the uniform dissipativity, strong linear stability and attraction basin conditions for sufficiently small ϵ , the solution u^ϵ of the time autonomous version of problem (2.1), (2.2) exists for all $t > 0$ and stays close to the solution of the shorted system (2.8), i.e.

$$u^\epsilon(x, t) = v(x, t) + \tilde{v}^\epsilon(x, t), \quad (3.6)$$

where the correction \tilde{v}^ϵ satisfies the estimate

$$|\tilde{v}^\epsilon(x, t)| < c\epsilon^s, \quad t \geq 0, \quad (3.7)$$

where $c > 0$ is a constant independent of ϵ , $s > 0$.

Furthermore, for sufficiently large times $t > t_\epsilon$ the following result holds:

$$u^\epsilon(x, t) = \phi(x) + \tilde{u}^\epsilon(x, t), \quad (3.8)$$

where $\tilde{u}^\epsilon(x, t)$ satisfies the following estimate uniformly in x :

$$|\tilde{u}^\epsilon(x, t)| < c_1\epsilon^2. \quad (3.9)$$

Proof. The proof uses the following Lemma, which is a slightly modified version of a comparison theorem for systems of reaction-diffusion equations [Smo83]. To formulate this Lemma, we introduce two sets depending on two vectors w^-, w^+ . We denote

$$E_+^i(w^+, w^-) = \{\xi | \xi_i = w^+, w^- \leq \xi_j \leq w^+, \forall j \neq i\},$$

$$E_-^i(w^+, w^-) = \{\xi | \xi_i = w^-, w^- \leq \xi_j \leq w^+, \forall j \neq i\}.$$

Lemma 3.1 Let $w(x, t) \in \mathbb{R}^n$ be the solution of problem (2.1), (2.2) with zero Neumann or periodic boundary conditions and initial data $w(x, 0) = w_0(x) \in \mathbb{R}^q$. Let the time dependent functions $w^+(t), w^-(t)$ satisfy

$$w_t^+ \geq \max_i \sup_{\xi \in E_+^i(w^+, w^-)} f_i(\xi, x),$$

$$w_t^- \leq \min_i \inf_{\xi \in E_-^i(w^+, w^-)} f_i(\xi, x), \text{ for any } x \in \Omega,$$

where $1 \leq i \leq n$.

Moreover, let us suppose

$$w^-(0) \leq w_i(x, 0) \leq w^+(0), \text{ for any } x \in \Omega.$$

Then

$$w^-(t) \leq w_i(x, t) \leq w^+(t), \text{ for any } t > 0, x \in \Omega.$$

To simplify the proof, we proceed with it in two parts, I and II. In the first part we show that $u_\epsilon(x, t)$ stays within distance $o(\epsilon^s)$ from the solution $v(x, t)$ of the shorted system for times $t < t_\epsilon = -a \log(\epsilon)$. We use the exponential decay of $v(x, t)$ to $\phi(x)$ in order to show that at $t = t_\epsilon$, the solution $u_\epsilon(x, t)$ is

within distance $o(\epsilon^s)$ from $\phi(x)$. In the second part we apply again the lemma and find that $u_\epsilon(x, t)$ remains within distance $o(\epsilon^s)$ from $v(x, t)$ for all $t \geq t_\epsilon$.

Part I. Let $w(x, t) = u_\epsilon(x, t) - v(x, t)$, where $v(x, t)$ is the solution of the shorted system with the same initial data as $u_\epsilon(x, t)$, $v(x, 0) = u_0(x)$.

Notice that the function w satisfies the equation

$$w_t = \epsilon^2 D \Delta w + f(v + w, x) - f(v, x) + \epsilon^2 g. \quad (3.10)$$

One has $|f(v + w, x) - f(v, x)| < C_2 |w|$ and $g = \Delta v$. Moreover, C^2 regularity of f and the initial data $u_0(x)$ imply that $|g| < C_1$.

Let us apply the comparison lemma to $w_t^+ = C_2 w^+ + C_1 \epsilon^2$, $w^+(0) = 0$, $w^-(t) = -w^+(t)$. From the relation $w^+(t) = C_1 C_2^{-1} \epsilon^2 (\exp(C_2 t) - 1)$ it follows that $|w(x, t)| \leq C_3 \epsilon^{2-C_2 a}$ for $t \leq t_\epsilon = -a \log \epsilon$ for positive a such that $C_2 a < 2$.

Now, using the spectral properties of the matrix $M(x)$ and the attractive nature of $\phi(x)$, we have

$$|v(x, t) - \phi(x)| < B \exp(-bt), t > T_0 \quad (3.11)$$

that holds uniformly for any $x \in \Omega$.

At $t = t_\epsilon$, one has $|v(x, t_\epsilon) - \phi(x)| \leq \delta \epsilon^{ba}$, hence $|u_\epsilon(t_\epsilon, x) - \phi(x)| \leq C_4 \epsilon^s$, where $\min(2 - C_2 a, ba) > s > 0$.

Part II. Let us define $\bar{w}(x, t)$ by $u_\epsilon(x, t) = \bar{w}(x, t) + \phi(x)$. Then \bar{w} satisfies the equation:

$$\bar{w}_t = \epsilon^2 D \Delta \bar{w} + M(x) \bar{w} + \epsilon^2 \Delta \phi + h(\bar{w}, x, t), \quad (3.12)$$

where $|h| \leq C_5 |\bar{w}|^2$.

From the C^2 regularity of f one obtains $|\Delta \phi| < C_6$. Let us choose w^+ to satisfy the equation

$$w_t^+ = -bw^+ + C_5 (w^+)^2 + C_6 \epsilon^2,$$

$w^+(t_\epsilon) = |u_\epsilon(x, t_\epsilon) - \phi(x)|$, and $w^-(t) = -w^+(t)$. Using the strong stability assumption on M , we find that $\max_i \sup_{\xi \in E_+^i(w^+, w^-)} \sum_j M_{ij} \xi_j \leq -bw^+$. This fact ensures that the function w^+ satisfies Lemma 3.1. The function w^+ is less than $c\epsilon^s$ at $t = t_\epsilon$ and $|w^+| < c\epsilon^s$ for all $t \geq t_\epsilon$. Thus $|u_\epsilon(x, t) - \phi(x)| < c\epsilon^s, t \geq t_\epsilon$. Together with estimate (3.11) this proves the first inequality (3.7). To prove (3.9), let us observe that estimate (3.7) can be improved as follows. Since $w^+ < c\epsilon^s$, we have

$$w_t^+ < -bw^+ + C_7 \epsilon^{s'} w^+ + C_6 \epsilon^2 < -\frac{b}{2} w^+ + C_6 \epsilon^2.$$

This implies that

$$w_+ < \bar{w}(t_\epsilon) \exp(-\frac{b}{2})(t - t_\epsilon) + 2C_1 b^{-1} \epsilon^2 (1 - \exp(-\frac{b}{2})(t - t_\epsilon)).$$

This completes the proof.

If $d_1 = d_2 = \dots = d_n = d$, this result can be improved. In this case the strong linear stability condition on $M(x)$ can be weakened. It is sufficient to suppose that the spectrum of $M(x)$ lies in the left half-plane for each x . More precisely, let us suppose that there holds the following

Weak linear stability assumption: For each fixed x the solution of the linear evolution equation

$$v_t = M(x)v,$$

satisfies the estimate

$$|v(t)| \leq |v(0)| \exp(-\sigma t), \quad \sigma > 0 \quad (3.13)$$

where σ is independent of x .

Theorem 3.2. Suppose that the conditions of Theorem 3.1, where the strong stability condition is replaced by the weak stability assumption, hold. Moreover, let the diffusion coefficients be equal

$$d_1 = \dots = d_n = d\epsilon^2 > 0. \quad (3.14)$$

Then, for sufficiently small ϵ , the solution u^ϵ of problem (2.1), (2.2) exists for all $t > 0$, stays close to a solution of shorted system (2.8) and satisfies the estimates (3.7), (3.9).

Proof. The first part of the proof repeats, without any changes, the proof of Theorem 3.1 (in fact, this part uses no properties of $M(x)$ excepting for (3.14)).

The second part must be modified and uses now the weak stability assumption and condition (3.14).

Let us consider again the equation

$$w_t = \epsilon^2 d \Delta w + M(x)w + \epsilon^2 g + h(w, x, t), \quad (3.15)$$

where $g = \Delta \phi$, $|h| < c|w|^2$. To estimate the solutions w of this equation, we introduce the matrix $W(x)$ of size $n \times n$ defined as follows [DK70]

$$W(x) = \int_0^\infty \exp(M(x)^\dagger t) \exp(M(x)t) dt.$$

This matrix is correctly defined since estimate (3.13) holds. The matrix W is symmetric and positively defined. Let (u, v) denote the inner scalar product in \mathbf{R}^n and $|u|$ is the norm. Then,

$$(Wu, u) = \int_0^\infty |\exp(M(x)t)u|^2 dt \leq \rho |u|^2, \quad \rho = \frac{1}{2\sigma} > 0$$

and the norms $|u|$ and $(Wu, u)^{1/2}$ are equivalents.

Moreover, let us notice that the definition of W entails [DK70]

$$WM + M^\dagger W = -I.$$

Let us define now a scalar function $R(x, t)$ by $R^2 = (Ww, w)$ and let us calculate the time derivative of this function for solutions w of equation (3.15). We obtain

$$\begin{aligned} \frac{1}{2}(R^2)_t &= d\epsilon^2[(W\Delta w, w) + (Ww, \Delta w)] + (W(h + \epsilon^2 g), w) + (w, W(h + \epsilon^2 g)) + \\ &\quad + (WMw, w) + (Ww, Mw). \end{aligned}$$

Notice that

$$(WMw, w) + (Ww, Mw) = -|w|^2.$$

Furthermore,

$$|(W(h + \epsilon^2 g), w) + (w, W(h + \epsilon^2 g))| \leq c_0 R^3 + c_1 \epsilon^2 R.$$

Let us consider the term $Y = (W\Delta w, w) + (Ww, \Delta w)$. This term can be represented as

$$Y = \Delta R^2 - 2(W\nabla w, \nabla w) - 2(\nabla W\nabla w, w) - 2(\nabla Ww, \nabla w).$$

Let us notice that

$$|(\nabla W\nabla w, w) + (\nabla Ww, \nabla w)| \leq c_2(\mu|\nabla w|^2 + \mu^{-1}|w|^2).$$

Let us choose μ such that $c_2\mu < \rho$. Then we find that

$$Y \leq \Delta R^2 + c_2\mu^{-1}|w|^2 \leq \Delta R^2 + c_3 R^2.$$

As a result, one obtains the differential inequality

$$\frac{1}{2}(R^2)_t \leq \epsilon^2 d\Delta R^2 + c_4 \epsilon^2 R + c_5 R^3 - R^2 \rho^{-1} + \epsilon^2 c_6 R^2, \quad t \geq t_\epsilon,$$

where $R(t_\epsilon) = c_7 \epsilon^s$, $s > 0$. By the standard scalar comparison principle [Smo83] this differential inequality implies that

$$R < c_8 \epsilon^{s'}, \quad s' > 0.$$

The theorem is proved.

To conclude this section let us notice that it is difficult to extend Theorem 3.1 to the case, where initial data lie in a attraction basin of a limit cycle or of a chaotic attractor. For the limit cycle case, there are formal asymptotic solutions, however, justification of these solutions is a difficult problem. Kuramoto [Kur84] has proposed the following asymptotic approach for the case $f = f(u)$. Supposing that shorted system (2.8) has a limit cycle solution $\phi(t)$, let us set

$$u^\epsilon = \phi(t + \theta(x, \tau)) + w, \tag{3.16}$$

where w is a small correction, $\tau = \epsilon^2 t$ is a rescaling time, θ is an unknown phase. Then, after some formal manipulations, one shows that the phase θ satisfies a nonlinear diffusion (Burgers) equation which in certain cases can be resolved analytically.

The proof of Theorem 3.1 shows that, in this case, the solution u^ϵ attains at a small neighborhood of the limit cycle within the time $\mathcal{O}(-\log \epsilon)$. However, a priori estimates do not work for all times. Furthermore, phase diffusion phenomena suggest that, in this case, one can expect a diffusion dependent patterning. Although the amplitude perturbation w is small, the phase perturbation θ is not small and it cannot be found by the shorted system.

Theorem 3.1 can be extended to the non-autonomous case, where f depends slowly on time but we omit these details.

4 Applications to genetic circuits

Diffusion neutral patterning is believed to be the main mechanism in the morphogenesis of the fruit fly [WBJ02]. We shall come back at the end of this section to the correctness of this point of view but let us first investigate its consequences here. In the fruit fly embryo, early development just after fecundation consists in antero-posterior differentiation of body segments. This patterning is essentially one-dimensional and it results from the interactions between maternal antero-posterior inducing morphogen gradients and a set of induced segmentation (gap) genes. The one-dimensional patterning dynamics has been studied in [RS95], where the gene circuit model is used (see section 2).

Let us consider how our approach works for the genetic circuits defined by equations (2.1), (2.4).

To begin with, let us notice that in the absence of diffusion the most general one-dimensional patterning dynamics is defined by a system of differential equations parametrized by the position $x \in \mathcal{K} \subset \mathbb{R}$, where \mathcal{K} is a compact interval. More precisely, the patterning dynamics is given by the functions $q_s(t, x)$ that satisfy the system:

$$\frac{dq_s}{dt} = Q_s(q, x), \quad q = (q_1, q_2, \dots, q_p) \quad (4.1)$$

defined on the unit ball $B_p \subset \mathbb{R}^p$ of dimension p , where the vector field $Q \in C^1(B_p \times \mathcal{K})$ and at the boundary this field is directed inward to B_p . Then for each x equations (4.1) define a global semiflow on B_p .

We say that a property of dynamics (4.1) is C^1 structurally stable, if each perturbed system (4.1)

$$\frac{dq_s}{dt} = Q_s(q, x) + \tilde{Q}(q, x), \quad (4.2)$$

such that $|\tilde{Q}|_{C^1(B_p \times \mathcal{K})} < \delta$ has the same property if δ is sufficiently small.

For example, the property to have a hyperbolic equilibrium is C^1 structurally stable (hyperbolicity means that the matrix of linearization at the equilibrium has no purely imaginary eigenvalues). Generally, the property to have an invariant hyperbolic set with a given topological structure is C^1 structurally stable (due to the theorem on the persistence of hyperbolic sets [Sma80, Rue89]). The property to have a locally attracting hyperbolic set is also C^1 structurally stable.

Gene circuit models lead to the following shorted equations:

$$(u_i)_t = \sigma_\alpha \left(\sum_{j=1}^n K_{ij} u_j + \sum_{k=1}^p J_{ik} m_k(x) - h_i \right) - \lambda_i u_i. \quad (4.3)$$

The following theorem expresses the fact that gene circuits models are sufficiently general as models for diffusion neutral patterning.

Theorem 4.1. *For each p , any system (4.1) and any $\delta > 0$ there exists such a choice of parameters n, K, m, h of the genetic circuit (4.3) such that the dynamics (4.3) has a globally attracting locally invariant manifold M_p of dimension p , for any $x \in \mathcal{K}$. This manifold is diffeomorphic to the p -dimensional unit ball B_p and the corresponding reduced dynamics is defined by the weakly perturbed system (4.2), where the perturbation satisfies $|\tilde{Q}|_{C^1(B_p \times \mathcal{K})} < \delta$.*

Therefore, the dynamics of shorted genetic equations (4.3) can have any C^1 structurally stable properties depending on a choice of n, K, m, h .

Proof. This theorem is a consequence of results in [Vak00, Vak02].

Remark. A too strong diffusion or a diffusion dependent patterning would impose restrictions on the structurally stable properties that can be reproduced by systems (2.1) with nonlinearities (2.5). We have already mentioned the phase diffusion phenomena for limit cycles. Also, for large diffusion coefficients the derivatives of the point attractors $u_\infty^\epsilon(x) = \lim_{t \rightarrow \infty} u^\epsilon(x, t)$ of system (2.1) with respect to x cannot take large values. Finally, diffusion may destabilize point attractors via the Turing mechanism. Turing instability is diffusion dependent patterning and is excluded by conditions (3.5) or (3.14).

Providing that all the hypothesis of Theorem 3.1 or 3.2 are fulfilled we can say that the introduction of diffusion has a small effect on patterning; patterning is diffusion neutral.

The main hypothesis of Theorems 3.1 and 3.2 refers to the structure of the attractors of the shorted equation that we shall analyze below.

The steady states of the shorted equation are solutions of

$$u_i = \lambda_i^{-1} \sigma_\alpha \left(\sum_{j=1}^n K_{ij} u_j + \sum_{k=1}^p J_{ik} m_k(x) - h_i \right) = G_i(u) \quad (4.4)$$

For large λ_i , the application $u \rightarrow G(u)$ is a contraction map and thus an unique stable rest point u_0 exists. In this case patterning is diffusion neutral. For smaller λ_i , it is possible to have coexistence of several point attractors. A necessary criterium for multi-stationarity is the existence of a positive loop in the interaction graph defined by the matrix K [Sou03]. For competitive gene circuits ($K_{ij} \leq 0$ for all $i \neq j$) such as the gap gene circuit of the fruit fly a positive loop means a loop made of an even number of interactions. As pointed out by Smale [Sma76] competitive systems in dimension n can have any dynamics that is possible in $n - 1$ dimensions. Chaotic attractors could be expected for $n \geq 4$ and limit cycles for $n \geq 3$. Competitive gene circuits for $n = 2$ have only point attractors and for $n = 3$ all attractors are either limit circles or points [Hir82, Hir90]. Cooperative gene circuits ($K_{ij} \geq 0$ for all $i \neq j$) are monotone and monotone systems have particularly simple dynamics: almost all trajectories converge to point equilibria [ST91]. Some gene circuits can be made cooperative just by a change of coordinates. It is the case of gene circuits such that any loop in the interaction graph has an even number of negative interactions.

Although there are no general methods for finding attractors, in some special cases there are algorithms allowing the exhaustive determination of point attractors. In the following we discuss such a special situation.

Let us consider the case $\alpha \gg 1$ and let us restrict for simplicity to the case of a single morphogen. Then the steady state solutions of the shorted equations have the following form as $\alpha \rightarrow \infty$:

$$u_i^0 = \lambda_i^{-1} s_i(x) + O(\alpha^{-1}), \quad s_i(x) \in \{0, 1\}. \quad (4.5)$$

Locally in x the steady state of the shorted equation are discrete and are indexed by the set $\{0, 1\}^n$. They are the solutions of the following binary programming

problem:

$$\sum_{j=1}^n \tilde{K}_{ij} s_j(x) + m(x) > \tilde{h}_i, \quad \text{if } s_i(x) = 1, \quad (4.6)$$

$$\sum_{j=1}^n \tilde{K}_{ij} s_j(x) + m(x) < \tilde{h}_i, \quad \text{if } s_i(x) = 0, \quad (4.7)$$

where $\tilde{K}_{ij} = \frac{K_{ij}}{J_{i1}\lambda_j}$, $\tilde{h}_i = \frac{h_i}{J_{i1}}$, $m(x) = m_1(x)$.

In the fruit fly embryo $m(x)$ is a monotonous function of the anteroposterior position x ($q = 1, x \in \mathbb{R}$). The solution of the programming problem can be given by specifying for each possible steady state $\mathcal{S}^{(k)} = (s_1^{(k)}, s_2^{(k)}, \dots, s_n^{(k)}) \in \{0, 1\}^n$ the domain $\mathcal{I}^{(k)}$ in x , where this state exists. If $m(x)$ is monotonous, then all $\mathcal{I}^{(k)}$ are intervals:

$$\mathcal{I}^{(k)} = \{x \mid \max_{s_i^{(k)}=1} (\tilde{h}_i - \sum_j \tilde{K}_{ij} s_j^{(k)}) < m(x) < \min_{s_i^{(k)}=0} (\tilde{h}_i - \sum_j \tilde{K}_{ij} s_j^{(k)})\}.$$

The pattern consists of segments corresponding to different states $\mathcal{S}^{(k)}$. If the intervals $\mathcal{I}^{(k)}$ have non-overlapping interiors, the interfaces separating segments are transition layers. Overlapping interval interiors are compatible with the presence of diffusion layers. As illustrated in Figure 4, the existence of diffusion layers may ask for extra conditions on the initial data or may be forced for all initial data.

In general, the binary programming problem is a very difficult problem for large numbers of genes. Nevertheless, early stages of morphogenesis correspond to a small number of interacting genes and the complete analysis of the problem is possible. Let us consider two examples of small complexity:

Example 1 : $n = 1$, one component.

In the gene circuit model, the one-component case describes the situation of a zygotic gene u_1 which is not regulated by other zygotic genes $u_j, j \neq 1$, i.e. $K_{1j} = 0$ for any $j \neq 1$.

In this case there are two possible steady states, $\mathcal{S}^{(1)} = (1), \mathcal{S}^{(2)} = (0)$, existing in the intervals $I^{(1)} = \{x \mid m(x) > \tilde{h}_1 - \tilde{K}_{11}\}$ and $I^{(2)} = \{x \mid m(x) < \tilde{h}_1\}$, respectively. If $K_{11} = 0$ (gene 1 has no regulation effect on itself) the two interval interiors do not overlap. The patterning is diffusion neutral. The interface between the two states is a transition layer and for $\epsilon \ll \alpha^{-1}$ its width is of order $\mathcal{O}(\alpha^{-1})$ (see Fig.2.1 a). This one-component case is the one usually used by biologists to illustrate Wolpert's positional information mechanisms [WBJ02] and the diffusion neutrality hypothesis is entirely justified here.

The case $K_{11} < 0$ (gene 1 inhibits itself) needs special treatment. Indeed, in this case there is a gap between the intervals $I^{(1)}$ and $I^{(2)}$ on which the boolean programming problem has no solution at all. This phenomenon is due to the singular character of the limit $\alpha \rightarrow \infty$ and disappears for finite α . Let us consider the function $f_\alpha(u, m) = \sigma_\alpha(K_{11}u + J_{11}m - h_1) - \lambda_1 u$. The function f is monotonic in m . The steady state of the shorted equation satisfies $f_\alpha(u, m) = 0$. If $m \in (\tilde{h}_1, \tilde{h}_1 - \tilde{K}_{11})$, then $f_\alpha(0, m) > 0$, $f_\alpha(1/\lambda_1, m) < 0$ and, therefore, there is an unique $u_0(m)$, $0 < u_0(m) < 1/\lambda_1$ such that $f_\alpha(u_0(m), m) = 0$. The function $\phi(x) = u_0(m(x))$ describes a smooth transition layer connecting the states $u_1 \mathcal{O}(\alpha^{-1})$ and $u_2 = 1/\lambda_1 + \mathcal{O}(\alpha^{-1})$. Patterning is diffusion neutral because

the branch of attractors $\phi(x)$ is unique. The pattern contains a transition layer whose width does not reduce to zero as $\alpha \rightarrow \infty$ (see Fig.2.1 b).

If $K_{11} > 0$ (gene 1 activates itself) there is an overlap of the intervals $I^{(1)}, I^{(2)}$ and it is possible to have type 2 interfaces (diffusion layers) and diffusion dependent patterning. In the last section we shall show that in this case the width of the interface is controlled by the diffusion coefficient D and that this width vanishes in the limit $\epsilon \rightarrow 0$ Fig.2.1 c,d. Fig.2.1 c illustrates a situation when the interval $I^{(2)}$ extends over the entire patterning domain. Depending on initial data patterning can be diffusion neutral or dependent. Initial data presented in Fig.2.1 c lead to a diffusion layer. Another choice of initial data $u_0(x) = 1$ (not shown in figure) would lead to a diffusion neutral steady state that has no interface. The case Fig.2.1 d does not leave this choice: irrespectively of data the pattern is forced to contain a diffusion layer and is diffusion dependent.

Example 2: $n = 2$, two components.

Let us suppose that $\tilde{K}_{ii} = 0, i = 1, 2, \tilde{K}_{12} \leq 0, \tilde{K}_{21} \leq 0$. In this case there are four possible steady states, $\mathcal{S}^{(1)} = (1, 1), \mathcal{S}^{(2)} = (0, 0), \mathcal{S}^{(3)} = (1, 0), \mathcal{S}^{(4)} = (0, 1)$. The corresponding existence intervals are $I^{(1)} = \{x | m(x) > \max(\tilde{h}_1 - \tilde{K}_{12}, \tilde{h}_2 - \tilde{K}_{21})\}$, $I^{(2)} = \{x | m(x) < \min(\tilde{h}_1, \tilde{h}_2)\}$, $I^{(3)} = \{x | \tilde{h}_1 < m(x) < \tilde{h}_2 - \tilde{K}_{21}\}$, $I^{(4)} = \{x | \tilde{h}_2 < m(x) < \tilde{h}_1 - \tilde{K}_{12}\}$. Notice that $I^{(3)}$ and $I^{(4)}$ can overlap if the following condition is satisfied:

$$\tilde{h}_1 \leq \tilde{h}_2 \leq \tilde{h}_1 - \tilde{K}_{12}, \quad \text{or} \quad \tilde{h}_2 \leq \tilde{h}_1 \leq \tilde{h}_2 - \tilde{K}_{21} \quad (4.8)$$

In general, existence of a diffusion layer connecting $\mathcal{S}^{(3)}$ and $\mathcal{S}^{(4)}$ depends on the initial data and on condition (4.8).

A diffusion layer always exists if an extremity of $I^{(3)}$ belongs to the interior of $I^{(4)}$, or reciprocally if an extremity of $I^{(4)}$ belongs to the interior of $I^{(3)}$. This condition corresponds to strict inequalities in (4.8).

The interiors of $I^{(1)}$, and of $I^{(2)}$ do not overlap on the interiors of other intervals, therefore the interfaces separating the states $\mathcal{S}^{(1)}$ or $\mathcal{S}^{(2)}$ from any other states are transition layers. Contrary to the preceding example, there are no longer gaps between intervals meaning that for small diffusion coefficients the widths of all the transition layers are of the order $\mathcal{O}(\alpha^{-1})$.

To conclude, in this case diffusion neutrality is justified for interfaces involving $\mathcal{S}^{(1)}$ or $\mathcal{S}^{(2)}$ but it is not always justified for interfaces separating $\mathcal{S}^{(3)}$ from $\mathcal{S}^{(4)}$.

5 Diffusion dependent patterning

If condition (3.3) of Theorem 3.1 is invalid, i.e., if initial data $u_0(x)$ lie in attraction basins of different attractors of the shorted system for different x , then the estimates of the previous section hold only on a time interval of order $\mathcal{O}(-\log \epsilon)$. The main reason for that is the following. In this case the derivatives of the solution $v(x, t)$ of the shorted equations with respect to x increase unboundedly at some fixed positions $x = q_0$ as $t \rightarrow \infty$. In the presence of diffusion, one can expect that there exist diffusion layers connecting different attractors of the shorted system. These layers are mobile. They eventually reach equilibrium positions which are generally different from the initial positions q_0 .

To understand this situation, let us remind some basic definitions from the theory of finite dimensional dynamical systems [Rue89]. Let us consider the

time autonomous shorted system (2.8) ($f = f(v, x)$) for a fixed $x \in \Omega$ and let us suppose that the uniform dissipativity condition holds in a ball $B(R_0)$ in \mathbf{R}^n . Let us recall that $u_0(x) \in B(R_0)$ is wandering if there exists a neighborhood $U(u_0)$ of u_0 and a time $T_0 > 0$ such that for all $t > T_0$ the trajectory $v(t, x, u_0(x))$ starting from $u_0(x)$ does not intersect $U(u_0)$: $v(t, x, u_0(x)) \notin U(u_0)$, $t > T_0$. In the theory of finite dimensional dynamical systems, the set of non wandering points play a key role [Rue89]. It is a closed invariant set which contains the ω -limit sets of all trajectories ($w \in \mathbf{R}^n$ is the ω - limit set of the trajectory $v(t, x, u_0(x))$ if and only if there is a sequence $t_k \rightarrow \infty$ such that $v(t_k, x, u_0(x)) \rightarrow w$ as $k \rightarrow \infty$). In our case these sets depend on x , since x plays the role of a parameter. Typically, the non wandering set Θ_x consists of some connected components A_x^i . Some components are local attractors (i.e., A_x^i attracts all trajectories starting in an open neighborhood of A_x^i), others are saddle sets and repellers. Intuitively, initial interface position can be associated with x such that the corresponding trajectory $v(x, t, u_0(x))$ goes to a saddle point or hangs in a fixed repeller as $t \rightarrow \infty$ [MV88].

However, a rigorous mathematical analysis is nontrivial even in the simplest cases. To illustrate, let us consider two simple examples. In these examples we set periodic boundary conditions in $x \in \Omega$, supposing that Ω is a box.

Example 1. Let us consider a system of Allen- Cahn's type:

$$u_t = \epsilon^2 \Delta u + a(x)(u - u^3), \quad u \in \mathbf{R}, \quad (5.1)$$

where $a(x) > 0$, $x \in \Omega \subset \mathbf{R}^q$. The nonwandering set of the shorted system is $\{-1, 0, 1\}$, where $1, -1$ are local attractors and 0 is a saddle point. If $u_0(x) > 0$ for all $x \in \Omega$ or if $u_0(x) < 0$ for all $x \in \Omega$, one can apply Theorem 3.1 or 3.2 and $u(t, x) \rightarrow \pm 1 + \mathcal{O}(\epsilon^s)$ as $t \rightarrow \infty$, respectively.

If there are points, where $u_0(x) = 0$, we can expect a more complicated behavior. The analysis [MV88] shows that the gradient of $u(x, t)$ increases to ∞ at the set $S = \{x : u_0(x) = 0\}$. Fife [FH88] described in detail the development of the inner layer in the one-dimensional case ($q = 1$) and when the set S contains a single point.

For arbitrary $u_0(x)$, the set S can be a rather complicated, fractal set. If $u_0 \in C^\infty$ and if the rank of the derivative $du_0(x)$ is r , $0 \leq r \leq q$ then by the implicit function theorem S is a smooth sub-manifold of Ω of co-dimension r . Like in [MV88], we use the concept of "generic situation", which is standard in differential topology [Hir76]. If the initial data u_0 are smooth and generic, $du_0(x)$ has full rank $r = 1$ (which is the dimension of the u -phase space), hence $\text{codim} S = 1$. This means that, within times t of order $|\log \epsilon|$, one obtains an interface appearance at some hypersurfaces in Ω . These hypersurfaces are initial positions for interface evolution for $t \gg O(|\log \epsilon|)$.

Example 2. Let us consider a system of Ginzburg -Landau's type:

$$u_t = \epsilon^2 \Delta u + a(x)(u - |u|^2 u),$$

where u is an unknown complex valued function, $a(x) > 0$ in Ω .

The non wandering set of the shorted system is the union of the attracting limit cycle $|u| = 1$ and the repeller $\{0\}$. The set S is now, for generic smooth $u_0(x)$, a submanifold of codimension 2. This means that if $\dim \Omega = 1$, generically, we have no singularity growth, if $\dim \Omega = 2$ one obtains vortices localized at some points and if $\dim \Omega = 3$ we have vortex lines [MV88].

Let us now formulate a result identifying the diffusion dependent patterning situation considered in the above examples.

Let us denote by $v(t, x, u_0(x))$ the solution of the time autonomous shorted system (2.8) with the initial data $u_0(x)$.

Let us formulate some conditions on dynamics of shorted system (2.8). Let us notice that among the components of Θ_x there exists a component $A_x \subset \Theta_x$ attracting a set B_x of points v with a non-empty interior. We denote by A'_x the complement of A_x in Θ_x . In the general case, the dependence of Θ_x and A_x on the parameter x may be very nontrivial. To simplify, we impose the following conditions:

C1 For each x the nonwandering set Θ_x of (2.8) contains a set A_x attracting for an open neighborhood V_x , $A_x \subset V_x$. This means that all the trajectories $v(t, x, v_0)$, starting at the points $v_0 \in V_x$ satisfy the condition:

$$\text{dist}\{v(t, x, v_0), A_x\} \rightarrow 0$$

as $t \rightarrow \infty$. Assume that V_x continuously depends on x , i.e.,

$$\text{dist}\{V_x, V_y\} \rightarrow 0$$

as $x \rightarrow y$.

C2 The sets A_x do not intersect the other components of the nonwandering sets Θ_y , i.e.,

$$A_x \cap A'_y = \emptyset$$

for any x, y .

The conditions on the attractors are fulfilled in the examples 1, 2 or more generally when $f(v, x)$ is scalar and has some continuous non-intersecting branches of roots $v_k(x)$, $k = 1, 2, \dots, M$, where $f_v(v_k(x), x) < 0$, serving as point attractors. It is the case of the Allen-Cahn model.

Theorem 5.1. Consider the time autonomous case $f = f(u, x)$, $f \in C^2$, where Ω is a box and we set the periodic boundary conditions. Assume that shorted system (2.8) satisfies the uniform dissipativity condition (3.2), and let the initial data satisfy

$$|u_0(x)| < R,$$

where R is the constant from the uniform dissipativity condition.

Suppose the shorted system satisfies conditions **C1**, **C2**. Suppose, moreover, that there exist two distinct points $x_0, x_1 \in \Omega$ such that the solutions of the shorted system satisfy

$$v(t, x_0, u_0(x_0)) \rightarrow A_{x_0},$$

and the ω -limit set of the trajectory $v(t, x_1, u_0(x_1))$ lies in the complement A'_{x_1} of A_{x_1} .

Then patterning with the initial data $u_0(x)$ is diffusion dependent.

Proof.

Let us suppose that patterning is diffusion neutral. Let us consider the set Ω_V consisting of $x \in \Omega$ such that the trajectory $v(t, x, u_0(x))$ enters V_x for some $t = t_0(x)$: $v(t_0, x, u_0(x)) \in V_x$. It is clear Ω_V is an open set since V_x depends continuously on x and trajectories $v(x, t, u_0(x))$ also depend continuously on

x within time bounded intervals. If $x \in \Omega_V$, the corresponding trajectory $v(t, x, u_0(x))$ of shorted system (2.8) converges to A_x . Indeed, this trajectory enters V_x , and since V_x is contained in the basin attraction of A_x , this trajectory tends to A_x as $t \rightarrow \infty$.

Let $\overline{\Omega}_V$ be the closure of Ω_V in Ω . As Ω_V is open in the connected set Ω , there exists a point x_* such that $x_* \in \overline{\Omega}_V$ and $x_* \notin \Omega_V$. Thus, for any $\delta > 0$ there exists $y_\delta \in \Omega_V$ such that $\text{dist}(y_\delta, x_*) < \delta$. Consider now the trajectories $v(t, y_\delta, u_0(y_\delta))$ and the trajectory $v(t, x_*, u_0(x_*))$. The first ones converge to the corresponding sets $A_{y_\delta} \subset V_{y_\delta}$. The trajectory $v(t, x_*, u_0(x_*))$ approaches to a ω -limit set C_* as $t \rightarrow \infty$ which does not intersect A_{x_*} . Thus this ω -limit set C_* lies in the complement A'_{x_*} . Therefore, this set C_* does not intersect any A_y for any y (due to assumption **C2**). Thanks to these limit properties of the trajectories $v(t, x_*, u_0(x_*))$ and $v(t, y_\delta, u_0(y_\delta))$ one concludes that, for sufficiently small $\kappa > 0, \delta > 0$ there is a time moment $T(\kappa, \delta)$ such that

$$|v(t, y_\delta, u_0(y_\delta)) - v(t, x_*, u_0(x_*))| > \kappa, \quad t = T(\kappa, \delta).$$

Let us choose a small ϵ such that $r_\epsilon < \kappa/2$. Let us fix such κ, ϵ . Then the previous estimate and the definition of diffusion neutral patterning yield

$$|u(t, y_\delta) - u(t, x_*)| > \frac{\kappa}{2}, \quad t = T(\kappa, \delta),$$

where $\text{dist}(y_\delta, x_*) < \delta$. This holds for any δ . Letting $\delta \rightarrow 0$ one notices that

$$|\nabla u(x_*, T(\kappa, \delta))| \rightarrow \infty \quad (\delta \rightarrow 0).$$

However, solutions of our problem (2.1), (2.2) are a priori bounded due to the uniform dissipativity. Therefore, the Schauder a priori estimate is fulfilled: $|u_x| < c\epsilon^{-1}$ [Kru66]. This fact gives us a contradiction with the last limit relation. The theorem is proved.

Now, let us describe some properties of diffusion layers. Unfortunately, there is not a general theory on such layers for $n > 1$. The diffusion layers can be described in the one-component case $n = 1$, and for $n > 1$ only in the case of gradient systems, or in the case of monotone systems [VVV94, VV96, VV99]. Let us remind that gene circuits generate a monotone dynamics if the interaction matrix K_{ij} satisfies the cooperativity condition $K_{ij} \geq 0, i \neq j$.

It is convenient to analyze the motion of internal layers in two steps. We shall only deal with the one-component case $n = 1$.

I. Internal (diffusion) layer problem in infinite homogeneous media

Let us ignore temporarily the dependence of f on the space variable x and on the slow time variable $\tau = \epsilon t$ and let us suppose that f has the shape in Fig. 2.1 c). This means that $f(u, x, \tau)$ satisfies the following assumptions (bistability): for each x, τ , the function $f(u, x, \tau)$ has only three roots $w_0(x, \tau), w_1(x, \tau)$ and $w_2(x, \tau)$ such that

$$f_u(w_0, x, \tau) < 0, \quad f_u(w_1, x, \tau) < 0, \quad f_u(w_2, x, \tau) > 0, \quad w_0 < w_2 < w_1, \quad (5.2)$$

for any x, τ .

Notice that this assumption is satisfied for the Allen-Cahn model. It is also satisfied for gene circuits under some conditions such as in the situation illustrated in Fig. 2.1 c).

Furthermore, let us consider that the pattern is infinite, i.e., $x \in (-\infty, +\infty)$. This leads to the following problem involving the parameters q, τ :

$$u_t = u_{xx} + f(u, q, \tau), \quad (5.3)$$

$$\lim_{x \rightarrow -\infty} u(x) = w_0(q, \tau), \quad \lim_{x \rightarrow +\infty} u(x) = w_1(q, \tau). \quad (5.4)$$

Denote by $\Phi(u, x, \tau)$ the primitive $\Phi(u, x, \tau) = \int_{w_0}^u f(s, x, \tau) ds$.

The well known result for this problem can be formulated as follows.

Proposition 5.2 *The internal (diffusion) layer problem (5.3), (5.4) has traveling wave solutions $u = \psi(x - V(q, \tau)t, q, \tau)$, where the velocity V is a functional of f (and thus depends on the parameters q, τ). The velocity $V(q, \tau) = 0$ if $\Phi(w_0, q, \tau) = \Phi(w_1, q, \tau)$. The function ψ is increasing in x for any fixed q, τ and satisfies the following exponential estimates*

$$|\psi(z) - w_0| < C \exp(b_0 z), \quad z < 0, \quad (5.5)$$

$$|\psi(z) - w_1| < C \exp(-b_1 z), \quad z > 0, \quad (5.6)$$

and

$$|\psi_z| < C \exp(-b|z|), \quad b = \min\{b_0, b_1\}, \quad (5.7)$$

where C, b_i, b are positive constants depending on q, τ .

Proof. Below we sometimes omit dependence on q, τ in notation. The function $\psi(\xi, q, \tau)$ satisfies the equation

$$\psi_{\xi\xi} + V\psi_{\xi} + f(\psi, q, \tau) = 0. \quad (5.8)$$

The existence of a solution of equation (5.8) satisfying exponential estimates is well known, for example, [FM77, VV96]. Multiplying equation (5.8) by ψ_{ξ} , replacing $f = \Phi_{\psi}$ and integrating one obtains :

$$\Phi(w_0) - \Phi(w_1) = \frac{V}{2} \int_{-\infty}^{\infty} (\psi_{\xi})^2 d\xi. \quad (5.9)$$

This equation shows that the velocity $V = 0$ and thus the traveling wave is a stationary interface if $\Phi(w_0) = \Phi(w_1)$.

Remark 1. If $V = 0$, equation (5.8) has a first integral $\frac{1}{2}\psi_{\xi}^2 + \Phi(\psi) = \Phi(w_0)$. This fact allows us to calculate the integral

$$\int_{-\infty}^{\infty} (\psi_{\xi})^2 d\xi = \sqrt{2} \int_{w_0}^{w_1} \sqrt{\Phi(w_0) - \Phi(\psi)} d\psi.$$

Thus, one obtains an approximate formula valid for small interface velocities:

$$V \approx \frac{\sqrt{2}[\Phi(w_0) - \Phi(w_1)]}{\int_{w_0}^{w_1} \sqrt{\Phi(w_0) - \Phi(\psi)} d\psi} \quad (5.10)$$

Remark 2. Constants b_i can be computed by a linearization of equation (5.3) at w_0 and w_1 respectively. We obtain

$$-V(q, \tau)b_i = b_i^2 + f_u(w_i, q, \tau) \quad (5.11)$$

Remark 3. This result can be generalized for monotone systems, see [VVV94, VV96, VV99]. However, even for weakly non-monotone systems this result is not correct: there are waves with a very complex structure, whose wave front profiles change with position and time [VV01]. For these examples the wave front cannot be presented as a function of $x - Vt$ and Proposition 5.2 does not hold; we shall not consider these questions here.

Example 1.

Let us consider the interface properties for a genetic circuit with a single zygotic gene and a single morphogen ($n = 1, K_{11} = 1, m(q) = J_{11}m_1(q) > 0, \lambda = \lambda_1, h = h_1$). Supposing that α (sharpness) is a large parameter, then for positions such that $h - 1/\lambda + \mathcal{O}(\alpha^{-1}) < m(q) < h + \mathcal{O}(\alpha^{-1})$ we obtain two stable stationary solutions ($u_- = \mathcal{O}(\alpha^{-1}), u_+ = \lambda^{-1} + \mathcal{O}(\alpha^{-1})$) and one unstable u_s defined by the relations $u_s = h - m + \alpha^{-1}v, \sigma(v) = \lambda(h - m + \alpha^{-1}v), |v| < C$.

In this case one has $\Phi(u) = (u + m - h)H(u + m - h) - \lambda u^2/2 + \mathcal{O}(\alpha^{-1})$, where H is the Heaviside step function. By this relation and (5.9) one finds

$$V(q) = \rho(q) \left[\frac{1}{2\lambda} - h + m(q) \right] + \mathcal{O}(\alpha^{-1}), \quad (5.12)$$

where $\rho > 0$ for all q . Using (5.10) one obtains the approximation $\rho(q) \approx 2\lambda\sqrt{2\lambda}$ valid for small velocities. We have a stationary interface if $m(q) = h - \frac{1}{2\lambda} + \mathcal{O}(\alpha^{-1})$.

Example 2.

The shorted equation of the Allen-Cahn model has two attractor nodes u_0, u_1 and a saddle u_2 . The values u_0, u_1 are the two maxima and u_2 is the minimum of the fourth order polynomial potential $\Phi(u)$. In this case the traveling wave velocity is

$$V(q, \tau) = \sqrt{2A(q, \tau)} [u_0(q, \tau) + u_1(q, \tau) - 2u_2(q, \tau)]. \quad (5.13)$$

There exist thus stationary interfaces, where the saddle is precisely at half distance between the two nodes:

$$u_2(q, \tau) = [u_0(q, \tau) + u_1(q, \tau)]/2. \quad (5.14)$$

II. Internal (diffusion) layer problem in heterogeneous media

After establishing Proposition 5.2, we can get a formal asymptotic solution of the interface motion problem. Let us set

$$u_{as} = \psi(\theta(x, t, \epsilon), q, \tau) + O(\epsilon), \quad (5.15)$$

where

$$\theta = \epsilon^{-1}(x - q(t)) \quad (5.16)$$

and where a unknown function $q(t)$ determines the localization of the narrow interface. By substituting the expression for u_{as} in equation (2.1) one observes that the terms of the principal order $O(1)$ vanish under the condition

$$\frac{dq}{dt} = \epsilon V(q, \epsilon t). \quad (5.17)$$

One can therefore expect that this equation describes the interface (diffusion layer) propagation. If f depends only on x , there exist stationary solutions of equation (5.17). Indeed, if q_1, q_2, \dots, q_l are roots of the function $V(q)$ then the diffusion layer is immobile in any one of the positions q_j . These equilibrium positions can be stable or unstable. It is easy to see that if the derivative $V'_q > 0$, then the corresponding position is unstable, and if $V'_q < 0$, the position is stable. In this situation there are stable stationary solutions with diffusion layers.

After this heuristic reasoning let us formulate the main result of this section.

Let us assume that the function f satisfies *uniform dissipativity* condition, namely, there exists positive constants M_1, M_2 uniform in x, τ such that

$$f(u, x, \tau) < 0, \quad u > M_1, \quad (5.18)$$

$$f(u, x, \tau) > 0, \quad u < -M_2. \quad (5.19)$$

This assumption ensures the existence of an unique smooth solution of (2.1) (see [Hen81]). Notice that the uniform dissipativity condition always holds for one-component genetic circuits. It also holds for the Allen-Cahn model if the functions $u_0(q, \tau), u_1(q, \tau)$ are uniformly bounded.

Theorem 5.3 (on the interface motion). *Let us consider the reaction-diffusion equation*

$$u_t = \epsilon^2 u_{xx} + f(u, x, \epsilon t), \quad u(x, 0) = u_0(x), \quad (5.20)$$

where $x \in [0, 1]$, under the zero Neumann boundary conditions

$$u_x(0, t) = u_x(1, t) = 0.$$

Assume $f \in C^2$. Let us suppose that the assumptions of Proposition 5.2 hold and

$$w_1(x, \tau) - w_0(x, \tau) > \delta_0 > 0,$$

$$\sup_{x, \tau} f_u(w_i, x, \tau) = -\mu_i < 0, \quad i = 0, 1, \quad (5.21)$$

where $x \in [0, 1]$, $\tau > 0$. Moreover, assume that

$$(w_0)_x(0, \tau) < 0, \quad (w_1)_x(1, \tau) > 0. \quad (5.22)$$

I. Let $\psi(\xi, q, \tau)$ be an interface solution of eq. (5.8) with asymptotic boundary conditions $\psi(-\infty, q, \tau) = w_0(q, \tau)$, $\psi(\infty, q, \tau) = w_1(q, \tau)$ (see Prop. 5.2). Suppose that the initial data are sufficiently close to this interface. More precisely,

$$|u_0(x) - \psi(\epsilon^{-1}(x - q_0), q_0, 0)| < \bar{c}_0 \epsilon^s, \quad s \in (0, 1), \quad (5.23)$$

Then, if ϵ is small enough, the solution of the problem has the interface form

$$u = \psi(\epsilon^{-1}(x - q(t)), q(t), \epsilon t) + v, \quad (5.24)$$

where the correction v satisfies the estimate

$$|v| < C \epsilon^s, \quad C > \bar{c}_0 > 0 \quad (5.25)$$

and the time evolution of the interface position q is defined by the differential equation

$$\frac{dq}{dt} = \epsilon(V(q, \epsilon t) + R(q, \epsilon, t)), \quad q(0) = q_0, \quad (5.26)$$

where

$$|R| < c' \epsilon^{s_1}, \quad s_1 > 0.$$

Equation (5.26) holds while $q > c\epsilon^{s_2}$ and $q < 1 - c\epsilon^{s_2}$, where $s_2 \in (0, 1)$.

II. Consider the time-independent case: $f = f(u, x)$. If there is a point q_* such that

$$V(q_*) = 0, \quad V'(q_*) < 0 \quad (5.27)$$

then there is a stationary, well localized at $x = q_*$ interface solution tending to a step-like function as $\epsilon \rightarrow 0$.

Remark 1. The assertion **II** is a consequence of results obtained by Fife [Fif89], who also considered the time evolution of interfaces in the case $f = f(u, x)$ [FH88].

Remark 2. Condition (5.22) is technical and simplify estimates.

Remark 3. Condition (5.21) yields that the functions $b_i, i = 0, 1$ defined by Eqs. 5.5, 5.6 satisfy;

$$b_i(x, \tau) > \tilde{b}_i > 0, \quad i = 0, 1,$$

for all $x \in [0, 1]$, $\tau > 0$.

Proof of part I. Below some key estimates can be simplified if w_0, w_1 are independent of x, τ . We reduce the general situation to this case by introducing a new variable \tilde{u} :

$$u = \beta(x, \tau)\tilde{u} + w_0(x, \tau), \quad \beta = w_1(x, \tau) - w_0(x, \tau), \quad (5.28)$$

where $\tau = \epsilon t$.

For the new unknown function \tilde{u} the corresponding values \tilde{w}_i are 0, 1, respectively. Moreover, the boundary conditions take the following form

$$\beta\tilde{u}_x(0, t) = -w_{0x}(0, \tau) - \beta_x(0, \tau)\tilde{u}(0, t), \quad (5.29)$$

$$\beta\tilde{u}_x(1, t) = -w_{0x}(1, \tau) - \beta_x(1, \tau)\tilde{u}(1, t). \quad (5.30)$$

Making the change $u \rightarrow \tilde{u}$ one obtains the equation

$$\tilde{u}_t = \epsilon^2 \tilde{u}_{xx} + \tilde{f}(\tilde{u}, x, \epsilon t) + \epsilon g_1(u, u_x, x, \epsilon t), \quad (5.31)$$

where

$$\begin{aligned} g_1(x, t, \epsilon) &= \beta^{-1}(\beta_\tau \tilde{u} + \epsilon \beta_{xx} \tilde{u} + 2\epsilon \beta_x \tilde{u}_x + \epsilon w_{0xx} - w_{0\tau}) \\ \tilde{f}(\tilde{u}, x, \tau) &= f(\beta \tilde{u} + w_0, x, \tau) \end{aligned} \quad (5.32)$$

We notice that $|g_1| < c$, with a constant c uniform in x, t, ϵ . Below, to simplify formulas, we omit the symbol tilde in notation.

To prove assertion **I**, we use the comparison principle [Fri64]. Our construction of a supersolution follows from [FM77], in a modified form, since here, with respect two [FM77], there are two additional difficulties: smallness of ϵ and the nonlinearity f depending on x, τ . Since $w_1 > w_0$, the function ψ defined by Prop. 5.2, is increasing in $\theta = \epsilon^{-1}(x - q)$ for all fixed τ, q and thus $\psi_\theta > 0$.

As a supersolution u^+ we take

$$u^+ = \psi(\theta, q, \tau) + \delta, \quad (5.33)$$

where δ is a small number, ψ is defined by Prop. 5.2 and satisfies

$$-V(q, \tau)\psi_\theta = \psi_{\theta\theta} + f(\psi, q, \tau). \quad (5.34)$$

The function q is defined by

$$\frac{dq}{dt} = \epsilon(V(q, \tau) - \delta_1), \quad q(0) = q_0, \quad (5.35)$$

where the "unperturbed" speed $V(q, \tau)$ is defined by Prop. 5.2. Both constants δ, δ_1 depend on ϵ .

Let us check that u^+ satisfies the comparison principle [Fri64]. We must check three main inequalities [Fri64]. The first, according to Theorem 17 (Chapter II) from [Fri64], at the boundaries $x = 0, 1$ our supersolution must satisfy the inequalities

$$\beta u_x^+(0, t) + w_{0x}(0, \tau) + \beta_x(0, \tau)u^+(0, t) < 0, \quad (5.36)$$

$$\beta u_x^+(1, t) + w_{0x}(1, \tau) + \beta_x(1, \tau)u^+(1, t) > 0. \quad (5.37)$$

One can check that, under the conditions $q > c\epsilon^{s_2}$ and $q < 1 - c\epsilon^{s_2}$, $s_2 \in (0, 1)$, both inequalities hold due to (5.22) and our explicit formula for u^+ . In fact, up to exponentially small corrections, the left hand side of inequality (5.36) is $(w_0)_x(0, \tau)$ and the left hand side of (5.37) is $(w_1)_x(1, \tau)$.

The second, at $t = 0$ our supersolution must majorize the initial data:

$$u^+(x, 0) > u_0(x).$$

This estimate holds due to relations (5.33), (5.35) and (5.23) if $\delta = C\epsilon^s$ and $C > \bar{c}_0$.

The third, it is necessary to check the following inequality:

$$0 > (V - \delta_1)\psi_\theta + \psi_{\theta\theta} + f(\psi + \delta, x, \tau) - \epsilon\psi_q(V - \delta_1) - \epsilon\psi_\tau + \epsilon g_1(\psi + \delta, \psi_x, x, \epsilon t). \quad (5.38)$$

Let us notice that

$$|\psi_\tau|, |\psi_q| < c.$$

Furthermore, by the Poincaré inequality we have $a\delta_0^2 < \int_{-\infty}^{\infty} \psi_\theta^2 d\theta$, $a > 0$ and by equation (5.9), one obtains $|V(q, \tau)| < b/\delta_0^2$.

Using the definition of ψ and the last estimates, let us replace inequality (5.38) by a stronger inequality

$$0 > -\delta_1\psi_\theta + f(\psi + \delta, x, \tau) - f(\psi, q, \tau) + C_1\epsilon. \quad (5.39)$$

This inequality can be rewritten as

$$0 > -\delta_1\psi_\theta + F_1 + F_2 + C_1\epsilon, \quad (5.40)$$

where

$$F_1 = f(\psi + \delta, x, \tau) - f(\psi, x, \tau),$$

$$F_2 = f(\psi, x, \tau) - f(\psi, q, \tau).$$

Let us introduce two domains Ω_1 and Ω_2 depending on t . The domain Ω_1 is an union of the two intervals

$$\Omega_1^+ = \{q < x < q - a_1 \epsilon \log \epsilon\}, \quad (5.41)$$

$$\Omega_1^- = \{q + a_0 \epsilon \log \epsilon < x < q\}, \quad (5.42)$$

and Ω_2 is a complementary domain

$$\Omega_2 = \Omega - \Omega_1. \quad (5.43)$$

Here the constants $a_i > 0$ are uniform in ϵ and will be chosen below together with δ, δ_1 .

We choose these parameters as follows:

$$\delta = C\epsilon^s, \quad \delta_1 = C_1\epsilon^{s_1}, \quad s, s_1 > 0,$$

where $C > \bar{c}_0$, the numbers s_1, s and a_i satisfy

$$s_1 < s < s_1 + a_1 \tilde{b}_1 < 1, \quad (5.44)$$

$$s < s_1 + a_0 \tilde{b}_0 < 1. \quad (5.45)$$

It is clear that, given positive \tilde{b}_i , such a choice of a_i, s_1, s is always possible. Below all constants C, C_k, c, c_k are uniform in ϵ as $\epsilon \rightarrow 0$.

Let us estimate F_2 . Suppose $x > q$. One has

$$|F_2| \leq |f_\xi(\psi, \xi, \tau)| |x - q|,$$

where $\xi \in [q, x]$. Since $f(w_1, q, \tau) = 0$ for any q and w_1 is independent of q (due to our assumption in beginning of the demonstration) one has $f_q(w_1, q, \tau) = 0$.

Thus the last estimate gives

$$|F_2| \leq c\epsilon |\psi(\theta, q, \tau) - w_1| |x - q|.$$

Using the exponential estimates $|\psi - w_1| < C \exp(-\tilde{b}_1 \theta)$ for the interfaces (see Prop. 5.2) and the fact that $\theta \exp(-\tilde{b}_1 \theta)$ is a bounded function on $(0, \infty)$, one has finally

$$|F_2| \leq c_1 \epsilon, \quad x > q.$$

The same inequality can be derived for $x < q$. Using this estimate, we replace main inequality (5.40) to a stronger inequality:

$$0 > -\delta_1 \psi_\theta + F_1 + C_2 \epsilon, \quad (5.46)$$

where C_2 is uniform in ϵ as $\epsilon \rightarrow 0$.

Let us turn into F_1 . Let $x > q, x \in \Omega_2$. We use now the following remark (see also [FM77]). If ρ is sufficiently small, for example, $|\rho| < r_1$, where r_1 is independent of ϵ , then

$$f_u(w_1 + \rho + \rho_1, x, \tau) < -\mu_1/2$$

for any $\rho_1 \in [0, \delta)$. Therefore, one obtains (due to our conditions on $f_u(w_1, x, \tau)$)

$$F_1 < -c_3\delta, \quad x \in \Omega_2, \quad x > q.$$

First let us consider (5.46) in the domain Ω_2 for $x > q$ (the case $x < q$ can be considered in a similar way). By replacing F_1 by its upper estimate one derives a stronger inequality

$$0 > C_2\epsilon - c_3\delta - \delta_1\psi_\theta.$$

This holds due to our choice of the parameter s and the interface monotonicity ($\psi_\theta > 0$), since for small ϵ one has $\delta = \epsilon^s$ and $\epsilon = o(\delta)$ as $\epsilon \rightarrow 0$.

Let us check inequality (5.46) in Ω_1^+ .

Thanks to the exponential asymptotics

$$\psi_{\theta\theta} = -\kappa(q, \tau) \exp(-b_1(q, \tau)\theta) + O(\exp(-2b_1\theta)), \quad \theta \rightarrow \infty,$$

where $\kappa > 0$, the function ψ is convex for sufficiently large θ , i.e.,

$$\psi_{\theta\theta}(\theta, q, \tau) < 0, \quad \theta > \theta_0(q, \tau).$$

Moreover due to (5.21) and the asymptotics $\psi(+\infty, q, \tau) = w_1$ of the interface ψ , there is a number θ_1 such that $F_1(\psi, x, \tau) < 0$ for $x > q + \epsilon\theta_1$. Let us set $\theta_2 = \max\{\theta_0, \theta_1\}$. Consider the subdomain W_+ of Ω_1^+ , where $x > q + \epsilon\theta_2$. In this domain $F_1 < 0$ and, due to the convexity $\psi_{\theta\theta} < 0$ in W , the function ψ_θ takes the minimal value at $x = q - a_1\epsilon \log \epsilon$.

Let us check now inequality (5.46) for the points $x \in W$. Due to this property of ψ , and our choice of s, s_1, a_1 , in W one has

$$C_2\epsilon < c\epsilon^{s_1+a_1\tilde{b}_1} \leq \delta_1\psi_\theta$$

for small ϵ . Since in this domain W one has $F_1 < 0$, main inequality (5.46) holds in W .

If $x \in \Omega_1^+$ and $x \notin W$, then $\psi_\theta > \kappa_0$, where $\kappa_0 > 0$ is independent of ϵ . Therefore, main inequality (5.40) again holds for sufficiently small ϵ . In fact, $|F_1| < c\delta$ and $F_1 + C_2\epsilon = o(\delta_1)$ as $\epsilon \rightarrow 0$ under conditions (5.44) and (5.45) on the choice s_1, s .

We have proved that the function u^+ is actually a supersolution. In a similar way, we can construct an analogous subsolution. Thus the theorem is completely proved.

Remark 2. There are situations where we need more delicate methods (than the comparison principle) to investigate the interface movement. Such situations occur when we study an interaction between many interfaces (see [Fus90, CP89, MV88]) or, for the metastability problem, $V(q) = 0$ for all q . The last case corresponds to $u_0 + u_1 \equiv 2u_2$ in the Allen-Cahn model. For the classical Allen-Cahn model with constant A, u_0, u_1, u_2 and zero Neumann boundary conditions it is known [CP89, Pin01] that interface solutions have exponential life times but that they unavoidably end up at the boundary. The result **II** does not hold in this case because $V'(q) = 0$. Interfaces can not satisfy the boundary conditions precisely. They do this only up to terms that are exponential in the distance between the interface and the boundary [Pin01]. This heuristic argument explains the attraction of interfaces by the boundaries.

More generally, it is known that the only stable solution of equation (5.20) with homogeneous function $f = f(u)$ and with Neumann no flux boundary conditions is homogeneous [Smo83].

Remark 3. The result **I** can be extended to the case when there is a number of different interfaces. If $f(u, x, \tau) = f(u)$, the case of many interfaces was studied in [CP89] and on a formal level, in [MV88].

6 Applications to shear banding and morphogenesis

6.1 Shear banding in pipe flow

Shear banding is an instability of complex fluids. It consists in the development of bands of different viscosities and shear rates when the fluid is sheared. To study flow of complex fluids the Navier-Stokes equations should be coupled to constitutive equations. In [ORL00, ROD03, ROL99] shear banding of worm-like micelles has been modelled by using the Johnson-Segalman constitutive model, see also [NPT90, BS94, MNB91]. Like in [EKL89] stress diffusion has been added to cope with transport of order parameter across inhomogeneous interfaces. In the (singular) limit of small Reynolds number the dynamics on time scales longer than the total stress equilibration time is described by a set of two reaction-diffusion equations. Unfortunately this system is neither gradient nor monotone, so the results of the preceding sections cannot be applied to it. In [ROL99] a toy model consisting of one reaction-diffusion equation has been used to mimic the basic properties of the phenomenon. Numerical simulations suggest that this equation has similar properties with respect to the existence and the propagation of kinks as the system yielded by the Johnson-Segalman model. In the Poiseuille (pipe flow) flow geometry the equation reads:

$$S_t = \epsilon^2 S_{xx} - S \left[1 + \left(\frac{\sigma(x, \tau) - S}{\eta} \right)^2 \right] + \frac{\sigma(x, \tau) - S}{\eta}, \quad \tau = \epsilon t, \quad (6.1)$$

where S is the part of the total shear stress carried by the micelles, ϵ^2 is the stress diffusion coefficient, $0 < \eta < 1/8$ is the retardation parameter, i.e., the ratio between the viscosity of the solvent and the viscosity of the micelles. σ is the total shear stress, which in the Poiseuille geometry depends linearly on the distance x orthogonal to the pipe axis $\sigma(x, \tau) = g(\tau)x$, the slow time function $g(\tau)$ is the pressure gradient that sustains the flow.

The shorted equation for this system is

$$S_t = f(S, \eta, \sigma) - S \left[1 + \left(\frac{\sigma - S}{\eta} \right)^2 \right] + \frac{\sigma - S}{\eta}. \quad (6.2)$$

If $0 < \eta < 1/8$, the third order polynomial $f(S, \eta, \sigma)$ has one real root which is a stable attractor for (I) $\sigma < \sigma_1(\eta)$, or (II) $\sigma > \sigma_2(\eta)$, and three real roots among which two stable attractors $S_0(\sigma), S_1(\sigma)$ and a saddle $S_2(\sigma)$ for (III) $\sigma_1(\eta) < \sigma < \sigma_2(\eta)$. One can notice that in the case (III) the model is equivalent to the Allen-Cahn model with the parameters $A = \frac{1}{\eta}$, $u_i = S_i(\sigma), i = 1, 3$.

Starting from the pipe axis σ increases with x and one passes from the situation (I) close to the axis to the situation (III) and eventually, if the pressure gradient is large enough to the situation (II) close to the pipe walls. Hence if $g > \sigma_1(\eta)/L$ where L is the half width of the pipe, an interface can form parallel to the pipe axis, separating bands of high (close to the axis) and low viscosity (close to the walls). The interface position q propagates according to the following (approximate) equation:

$$\frac{dq}{dt} = \sqrt{\frac{2D}{\eta}} [S_0(g(\tau)q) + S_1(g(\tau)q) - 2S_2(g(\tau)q)]. \quad (6.3)$$

If g is not time dependent the interface will be at rest in the position q_* satisfying $S_0(gq_*) + S_1(gq_*) - 2S_2(gq_*) = 0$. If such a position does not exist, steady flow will not be banded. If such a rest point exists, then the asymptotic relaxation of the interface position is exponential $q - q_* = C_1 \exp(-t/\tau)$, with $\tau^{-1} = \sqrt{\frac{2D}{\eta}} g[S'_0(gq_*) + S'_1(gq_*) - 2S'_2(gq_*)]$. This relation has been used in [ROD03] to estimate D from rheological measurements.

6.2 Segmentation of the fruit fly

Let us come back to the examples analyzed in the section 4 and let us discuss the situations involving diffusion dependent patterning. The remark from the previous section applies here as well: excepting the case of monotonous systems $K_{i,j} \geq 0, i \neq j$ there are no rigorous results in the case of several components ($n > 1$). One could use matched asymptotic techniques in order to obtain interface velocity estimates for $n > 1$ in the limit $\alpha \rightarrow \infty$, but this is cumbersome and will not be discussed here. To illustrate our method and concepts we shall only refer to the case of one component ($n = 1$).

Example

In the gene circuit model with $n = 1$, bistable interface and diffusion dependent patterning are possible if $K_{11} > 0$ (gene 1 activates itself). In this case the interiors of the intervals $I^{(1)}, I^{(2)}$ overlap. Let $I^{(3)} = I^{(1)} \cap I^{(2)} = \{x | \tilde{h}_1 - \tilde{K}_{11} < m(x) < \tilde{h}_1\}$. On the interval $I^{(3)}$ the attractor $S^{(1)} = (1)$ coding for $u_- = \mathcal{O}(\alpha^{-1})$ and the attractor $S^{(1)} = (1)$ coding for $u_+ = \lambda^{-1} + \mathcal{O}(\alpha^{-1})$ coexist. An interface of width of order $\mathcal{O}(\epsilon)$ (where $\epsilon = \sqrt{D}$, D being the diffusion coefficient) exists at a position $q \in I^{(3)}$. Strictly speaking we have proven Theorem 5.2 only in the case when $I^{(3)}$ extends across the entire domain of x . This avoids dealing with the extremities of $I^{(3)}$ which are turning points. If this extra condition is satisfied, we can apply Theorem 5.2 and equation (5.12) giving the kink velocity to obtain the following approximate equation for the position of the interface:

$$\frac{dq}{dt} = 2\lambda\epsilon\sqrt{2\lambda}\left[\frac{1}{2\lambda} - h + m(q)\right]. \quad (6.4)$$

The interface is at rest at a position q_* such that:

$$m(q_*) = h - \frac{1}{2\lambda}. \quad (6.5)$$

We should warn the biologist reader that this result is valid asymptotically in the small diffusion limit $\epsilon \rightarrow 0$. It implies that reaction and diffusion time

scales are well separated. In this case only, first a kink forms in a position depending on initial data and then this moves slowly according to the equation 6.4 (see also [FH88]). If the two time scales are not separated (large diffusion coefficient) then the kink forms and finds its position in the same time. For large diffusion, the equilibrium position can be shifted from the position given by Eq. 6.5.

6.3 Biological and physical consequences

Our results on diffusion dependent patterning do not conflict Wolpert's concept of positional information. Actually, they add quantitative precision to it. Theorem 5.3 (see equations (5.27, 6.5)) backs up Wolpert's theory of pattern formation: the equilibrium positions of the interfaces between segments are functions of the morphogens levels. The difference between our results and Wolpert's theory lies at the level of dynamical details, most particularly in the diffusion dependent case.

Diffusion neutral patterning does not need diffusion to function. If the unique attractor condition (3.3) is satisfied, then the pattern is independent on initial data. Wolpert's threshold mechanism for positioning interfaces explains the essential features of patterning.

The major difference between our results and Wolpert's theory occurs in the diffusion dependent case. In this case, there are two new features: a) patterning is dependent on initial data and in certain cases this dependence is discontinuous (the Cauchy problem is ill posed); b) diffusion partially or totally removes the ill posedness of the Cauchy problem. Let us explain in more details these new features.

As discussed in the beginning of Section 5, without diffusion, interfaces form in positions where initial data are saddles or repellers of the shorted equation. For instance, the solutions of the Allen-Cahn model with small initial data and no diffusion may contain an arbitrary number of bands and of interfaces. Diffusion partially lifts this degeneracy. According to Theorem 5.3, stationary interfaces choose well defined positions. Furthermore, under the uniform dissipativity condition 3.2, the solutions of the full system depend continuously on initial data on bounded time intervals. Nevertheless, at short times, the distance between the solution of the full system and the solution of the shorted system can be small (excepting for neighborhoods of the interfaces by Theorem 5.2). In practical situations when the asymptotic dynamics can not be observed or has no biological meaning, the regulatory effect (the new feature b)) of diffusion can be hard to prove.

The sequence of bands and interfaces is robust in early [KL91] and also in later stages patterning [vDMMO00] of *Drosophila*. This observation does not exclude diffusion dependent mechanisms. Indeed, even in the diffusion dependent case, early and asymptotic sequence of attractors can be identical if initial data is judiciously chosen, i.e. by ensuring the right amounts of maternal proteins. The allowable error for this choice depends on the size of the attraction basins. Diffusion dependent reasonings could explain experimental findings [KS97] showing that the level and timing of gene expression as well as protein diffusion have consequences on patterning.

Another refinement of Wolpert's theory concerns the structure of the interfaces. Transition layers have widths that depend on the steepness of the

sigmoidal function describing gene interaction. Biologists quantify this steepness by the so-called Hill coefficient [HWL02]. Very steep interfaces between patterning segments were observed at the end of the segmentation process of *Drosophila* [HWL02]. Nonetheless, it is difficult to explain an unbounded increase of the Hill coefficient. On the contrary, widths of diffusion layers do not depend on the steepness of the interactions but on the diffusion coefficients. Diffusion coefficients and diffusion layers widths can be decreased drastically by crowding effects.

In phase transitions of complex fluids, the dynamical characteristics of diffusion dependent patterning were proven experimentally [ROD03]. These include multiscale dynamics, metastability, and reproducible selection (independent on initial data) of the steady state.

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